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Correlation of culture with histopathology in fungal burn wound colonization and infection☆

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ABSTRACT

An increasing number of burn wound infections are now due to fungi. Historically, therapy of fungal burn wound infections (FWI) consisted of debridement, topical antifungals and/or IV amphotericin B, negating the need to categorize disease further than fungal burn wound colonization (FWC) versus FWI. Newer antifungal agents have varying spectrums of activity, increasing the importance of identifying fungi, often to species. The records of patients admitted to our burn center from April 2000 to March 2005 were reviewed for fungi identified by histopathology. Wound specimens with fungi were classified as FWC or FWI and culture results were compared. The 1515 surgical wound tissue specimens were obtained from 2036 patients. Fungi were detected in the histopathology of 68 patients, 19 with FWI (3.8 FWI/year); 9 had corresponding growth on culture. Forty nine patients were identified with FWC, 16 with fungi recovered in corresponding cultures. FWI was associated with increased mortality (OR 25.3, CI 3.12–204.8). Correlation between histopathologic and culture identification of fungi was inconsistent. The etiology of FWI was diverse; fungi with known resistance to each of the three major classes of antifungals were isolated, suggesting empirical use of one class may be inadequate to treat FWI. Future burn wound management must seek to identify fungal pathogens to species.

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1. Introduction

Burn wound infections remain an important source of morbidity and mortality in burn centers. In the past, the predominant pathogens were bacterial, but with advancements in burn wound care and the introduction of topical mafenide in 1964, the epidemiology of burn wound infections has shifted such that fungal pathogens are now more common. In the years subsequent to the introduction of mafenide (1964–1969), the United States Army Institute of Surgical Research (USAISR) noted a four-fold increase in incidence of fungal burn wound infections (FWI) [1]. In a follow on study, this trend continued with the yearly incidence of bacterial wound infections decreasing while the incidence of FWI remained unchanged [2]. During this second time period fungi represented the most common burn wound pathogens.

Recovery of fungi in culture from wounds can be difficult. In the past, identification to genus and species was of limited importance, as therapy consisted mainly of surgical intervention and intravenous amphotericin B (or topical antifungal

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Table 1 – Spectrum of activity of currently available systemic antifungal drugs

Drugs	Spectrum	Fungi with proven clinical or in vitro resistance	Fungi with reports of clinical resistance or decreased in vitro susceptibility[a]
Polyene			
Amphotericin B[b]	Most yeasts and moulds	*Aspergillus terreus*, *Scedosporium* (*Pseudallescheria*) species, *Candida lusitaniae*	*Fusarium*, *Trichosporon*
Azole			
Fluconazole	Most yeasts	Most moulds, *Candida krusei*	*Candida glabrata*
Itraconazole	Most yeasts and moulds	Zygomycetes	*Fusarium*
Voriconazole	Most yeasts and moulds	Zygomycetes	
Echinocandin			
Anidulafungin, caspofungin, micafungin	Candidal yeasts and *Aspergillus*	Zygomycetes, *Cryptococcus*, *Trichosporon*, *Fusarium*	*Candida parapsilosis*, *Candida guilliermondii*

[a] At least in some strains or clinical isolates.
[b] Includes lipid formulations of amphotericin B.

compounds). FWI have previously been identified and classified by wound histopathology. The introduction of systemically available azoles (fluconazole and itraconazole), and more recently, the broad-spectrum azole voriconazole and the echinocandins (anidulafungin, caspofungin and micafungin), has greatly impacted the treatment of fungal infections in general. The newest of these agents are effective against a wide range of fungi; however, none of them cover all potential pathogens (Table 1). Although amphotericin B still has the broadest spectrum of all antifungal agents, these newer agents do provide coverage against several fungi that are not typically responsive to amphotericin B (e.g., *Pseudallescheria boydii* and *Aspergillus terreus*).

Identification of the genus (and often species) causing FWI has become important for patient care, as no one agent can provide adequate empirical therapy in all infected patients. Herein, we review and compare the culture recovery and histopathological diagnosis of FWI and fungal burn wound colonization (FWC) at our institution over a 5-year period to examine the correlation between these methods and its impact (or potential impact) on selection of antifungal therapy.

2. Methods

All patients admitted to the USAISR burn center from April 1, 2000 to March 30, 2005 were identified. Electronic medical records, the USAISR research database, and histopathology reports were reviewed to select those patients with FWC or FWI. For those identified, demographic details were collected, including age, sex, total body surface area (TBSA) burn and select comorbidities (diabetes mellitus, hypertension, malignancy, alcohol abuse). Survival to discharge or death was also recorded for each patient. Research was conducted under an Institutional Review Board approved protocol.

Wound histopathology reports from all identified patients were reviewed for presence and description of fungi microscopically. Tissue specimens were obtained both routinely with excision and grafting operations, as well as when wound infection was suspected. Autopsy reports were also reviewed, when available. Patients with fungi found on histopathology were further classified as having colonization or infection based on the system developed at the USAISR [3]. FWC was defined as observation of fungal elements in the burn eschar

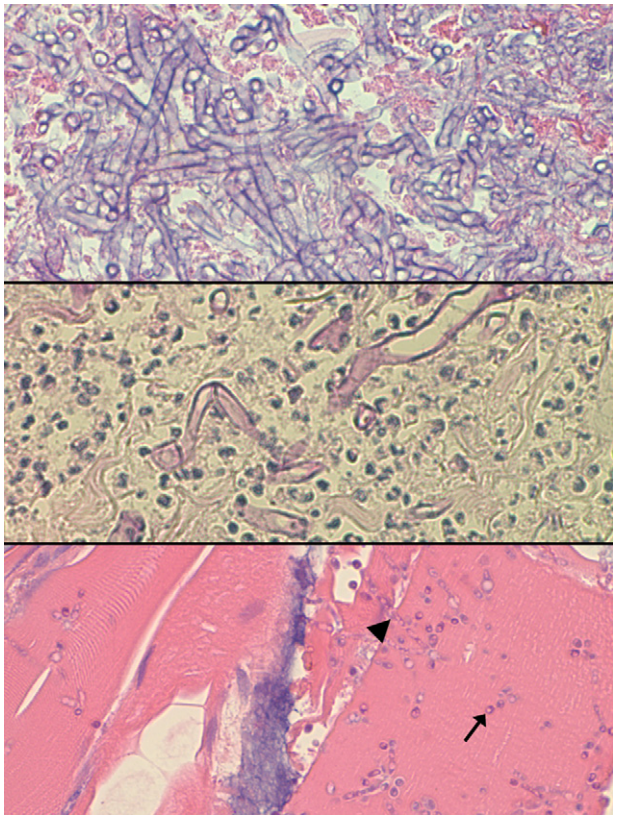

Fig. 1 – Fungi causing fungal burn wound infection are grouped based on histopathological characteristics. *Aspergillus*-like morphology (top panel); presence of parallel-walled, branching, septate hyphae, *Mucor*-like morphology (zygomycosis/mucormycosis) (middle panel); presence of wide, ribbon-like, rarely septate hyphae or Yeast-like morphology (bottom panel); presence of budding yeasts or rounded, Yeast-like structures (arrow), with or without septate or pseudohyphae (arrow head).

without penetration to the level of viable tissue. FWI was defined as invasion of fungi into the viable tissue below the eschar in a specimen. Reported morphology of fungi in tissue was grouped into three categories: (1) *Aspergillus*-like morphology; presence of parallel-walled, branching, septate hyphae, (2) *Mucor*-like morphology (zygomycosis/mucormycosis); presence of wide, ribbon-like, rarely septate hyphae and (3) Yeast-like morphology; presence of budding yeasts or rounded, yeast-like structures (many yeasts including most *Candida* species also produce hyphae and pseudohyphae in tissue) (Fig. 1). Fungal culture results were reviewed and matched based on anatomic site and date of culture with histopathology results. Material sent for fungal culture during this time period was not standardized, and included surgically obtained tissue as well as swabs of wounds. Recovery of fungi in the clinical mycology laboratory was performed using standard methods, including mycologic media both with and without inhibitory antimicrobial agents.

Univariate analysis was first used to compare the relationship of different risk factors to mortality such as age, gender, TBSA burn and fungal wound colonization versus infection. The Chi-square test was used for categorical variables and the Student's *t*-test was used for continuous variables. All variables found to be associated with a $p < 0.1$ were included in a multivariate logistic regression model of mortality. All statistical analyses were performed using SPSS Version 13.0 (SPSS, Chicago, IL) with $p < 0.05$ accepted as statistically significant.

3. Results

During the period from April 1, 2000 to March 30, 2005, 2036 patients were admitted to the USAISR burn center. Of 1515 surgical specimens examined by histopathology, 68 contained fungi, 19 of which were consistent with a diagnosis of FWI (3.8 FWI/year) (Table 2). This represents an incidence of FWI of 0.69 per 1000 hospital days or 12.1 per 1000 discharges during the defined study period. Over the study period, the incidence of FWI ranged from 1 to 5 per year, with per 1000 hospital day rates of 0.58 and 0.52 during 2004 and the first 3 months of 2005, respectively. The majority of patients with both colonization and infection were less than 50 years of age and male. Overall, the prevalence of studied comorbidities in our population was quite low. The median TBSA for patients with FWC was significantly less than that of those with FWI ($p = 0.046$).

Overall mortality in both univariate (OR 8.63, CI 2.57–28.98) and multivariate (OR 25.3, CI 3.12–204.8) analysis of patients with FWI was significantly higher than that seen in those with FWC. Other factors such as age and TBSA burn also contributed to an increased mortality per unit (either per year or per % surface area) in the multivariate analysis but to a lesser extent, odds ratios of 1.12 (CI 1.04–1.20) and 1.10 (CI 1.03–1.17), respectively. Male gender was associated with a significantly lower odds of death (OR 0.10, CI 0.01–0.80). Autopsy was performed in 17 patients. Of these, invasive fungal disease was identified as a contributing cause of death in three patients, all of which were identified as having FWC on pre-mortem burn wound histopathology. Five other patients had fungi identified on post-mortem histopathology, but in none of these was this identified as a contributing cause of death. Of the five, four were identified with FWI on pre-mortem wound histopathology while the fifth was identified as FWC.

Of the 68 patients identified with fungi on wound histopathology, 25 patients were identified as having 36 specimens with corresponding growth in culture. Twenty-three of these specimens were found to have *Aspergillus*-like morphology on histopathology (Table 3). All cultures corresponding to these 23 specimens recovered fungi that can produce this morphology in tissue. Fifteen corresponding cultures recovered an *Aspergillus* species; nine grew *Aspergillus* species alone and the remaining six grew multiple genera, which included *Aspergillus*. The remaining eight cultures grew fungi other than *Aspergillus*, including *Fusarium* and *Candida*

Table 2 – Demographic characteristics of patients with burn wound histopathology positive for fungal colonization or infection

Characteristic	Total ($n = 68$)	Fungal wound colonization ($n = 49$)	Fungal wound infection ($n = 19$)
Median age (range)	41 (11–74)	42 (11–88)	33 (19–74)
Male gender	55	41	14
Comorbid conditions			
DM	7	6	1
HTN	10	7	3
Cancer	2	2	0
Alcohol abuse	2	1	1
Median % TBSA burn (range)	48 (4–95)	39 (4–95)	63[a] (35–85)
Mortality			
Overall (%)	40	24	79
<50 years old (%)	35	18	79
>50 years old (%)	50	40	90
Men (%)	35	22	71
Women (%)	62	38	100

DM, diabetes mellitus; HTN, hypertension; TBSA, total body surface area.
[a] *p*-Value 0.046 for colonization vs. infection.

Table 3 – Correlation of culture results with microscopic morphology found on burn wound histopathology

Wound histopathology[a]	Corresponding wound culture
Parallel, branching, septate hyphae (*Aspergillus*-like morphology) *n* = 23 specimens, 18 patients	*Aspergillus* sp only—9
	Fusarium sp only—5
	Candida albicans only—1
	Aspergillus sp + *Trichosporon* sp + *Candida glabrata*—1
	Aspergillus sp + *Fusarium* sp + *Mucor* sp—1
	Aspergillus sp + *Fusarium* sp—1
	Aspergillus sp + *Mucor* sp—1
	Aspergillus sp + *Bipolaris* sp—1
	Aspergillus sp + *Trichosporon* sp—1
	Fusarium sp + *Trichosporon* sp—1
	Curvularia sp + *Candida parapsilosis*—1
Wide, ribbon-like, non-septate hyphae (*Mucor*-like morphology, zygomycosis/mucormycosis) *n* = 5 specimens, 4 patients	*Mucor* sp + *Fusarium* sp + *Paecilomyces* sp—1
	Mucor sp + *Aspergillus* sp—1
	Alternaria sp only—1
	Candida albicans only—1
	Paecilomyces sp only—1
Yeast-like organisms (Yeast-like morphology) *n* = 8 specimens, 7 patients	*Candida* sp only[b]—5
	Candida albicans + *Aspergillus terreus*—1
	Candida parapsilosis + *Fusarium* sp—1
	Fusarium sp only—1

[a] Data from 25 patients with 36 wound histopathology specimens with corresponding burn wound cultures.
[b] Candida species were *Candida albicans* (*n* = 4) and *Candida parapsilosis* (*n* = 1).

species. Pathology specimens containing fungi with *Mucor*-like morphology (zygomycosis/mucormycosis) grew *Mucor* species mixed with one or two other fungi in 40%. The remaining cultures grew *Alternaria* species, *Candida albicans* and *Paecilomyces* species without recovery of a Zygomycete. Finally, those surgical specimens found to have Yeast-like organisms on histopathology grew *Candida* species the majority of the time; however, a *Fusarium* species was recovered alone in one corresponding culture.

Overall the death rate for patients with *Candida* species by culture was 60%, not statistically different compared with a death rate of 66.7% for those with mould species by culture, $p = 0.729$ (Table 4). In the patients with *Candida* species by culture, there was no statistically significant difference in mortality between those with FWC and those with FWI. In addition, there was no difference in mortality between patients with *C. albicans* compared with non-*albicans* species, $p = 0.326$.

Of the patients with mould species, the majority had an *Aspergillus*, followed by *Fusarium*, *Trichosporon*, and *Mucor* species. Of those with *Aspergillus*, six patients grew *A. terreus*. For patients with *Aspergillus* species by culture there was no statistical difference in mortality when comparing FWI to FWC. Mortality was 100% in patients with *Mucor*, *Alternaria*, *Bipolaris*, *Curvularia* or *Paecilomyces* species; 90% in those patients with *Fusarium* species.

4. Discussion

Fungal wound infections remain an important source of morbidity and mortality in burn units. In an early case series of 30 patients admitted to this institute from 1954 to 1970, there was a 50% overall mortality with a 30% attributable mortality for invasive fungal infections [4]. A later review from the USAISR reviewed cases of fungal burn wound infections from 1973 to 1977. Mortality was 83% in those treated for invasive candidal infections and 87% for treated non-candidal invasive fungal infections [5]. A later retrospective review at Ohio State University revealed five patients with fungal burn wound sepsis with a mortality of 60% [6]. A 10-year review of patients with fungal burn wound infection at the USAISR from 1979 to 1989 studied 141 fungal burn wound infections diagnosed by histopathology. Mortality in this series was 74.5%. It was noted over the study period that the yearly incidence of bacterial wound infections continued to decrease, while that for fungal burn wound infections remained stable and represented the most common type of burn wound infection [2].

Researchers have associated this trend with the introduction of topical mafenide (a drug with limited antifungal activity) in 1964. A follow-up retrospective histological review of post-mortem examinations from 1960 to 1969, periods before and after the institution of mafenide, was undertaken. This showed an increase both in fungal colonization of burn wounds as well as deep invasion. The incidence of deep fungal infection increased four-fold from 1964 to 1969 in this study [1]. More recently a study from 1993 of data from the National Nosocomial Infections Surveillance System revealed that the rates of nosocomial fungal infections increased between 1980 and 1990. The overall rate of fungal surgical wound infection increased from 1.0 to 3.1 per 1000 discharges. For the later period from 1986 to 1990, the study specifically focused on units with the highest rates of infection and showed that the burn/trauma unit had the highest rate of nosocomial fungal infections at 16.1 per 1000 discharges [7]. We found an incidence of FWI of 12.1 per 1000 discharges, which is lower

Table 4 – The mortality associated with fungal organisms recovered from burn wound colonization and infections

Culture results	Total	Fungal wound colonization	Fungal wound infection
CANDIDA[a]	10	7	3
Deaths	6 (60)	4 (57)	3 (100)
C. albicans	6	4	2
Deaths	3 (50)	1 (25)	2 (100)
Non-*albicans Candida*	5	3	2
Deaths	4 (90)	2 (67)	2(100)
MOULDS[b]	19	12	7
Deaths	12 (63)	5(42)	7 (100)
Aspergillus	13	8	5
Deaths	8 (62)	3 (38)	5 (100)
A. fumigatus	4	3	1
A. terreus	6	2	4
A. flavus	2	1	1
A. nidulans	1	1	0
Unspeciated	1	1	0
Mucor sp	2	0	2
Deaths	2 (100)	0 (0)	2 (100)
Hyalohyphomycoses	7	5	2
Deaths	6 (86)	4 (90)	2 (100)
Fusarium sp	6	5	1
Paecilomyces sp	1	0	1
Phaeohyphomycoses	3	1	2
Deaths	3 (100)	1 (100)	2 (100)
Alternaria sp	1	0	1
Bipolaris sp	1	1	0
Curvularia sp	1	0	1
Trichosporon sp	3	2	1
Deaths	3 (100)	2 (100)	1(100)

Values in parentheses are percentages.
[a] Multiple patients had two or more species of *Candida* from wound culture.
[b] Multiple patients had multiple different moulds from wound culture.

than previous reports likely related to our strict definition of FWI as having a surgical specimen with histopathology showing invasion of fungal elements into viable tissue and not just a positive culture [2,4–6,8,9]. In spite of the lower prevalence of FWI, our study highlights the importance of this entity as the presence of fungal wound infection carried a very high risk of death in our population.

With the continued problem of fungal wound infections and the introduction of newer antifungal therapies, accurate microbiological diagnosis of fungal burn wound infections has become increasingly important. No antifungal provides optimal coverage for all fungi (Table 1). Traditional amphotericin products have good coverage of most *Candida* and *Aspergillus* species, but have inconsistent activity against *A. terreus*, *P. boydii* and *Trichosporon* species. Although decreased in their lipid-based formulations, all amphotericin-containing products have treatment-associated toxicities. The older azole agents, fluconazole and itraconazole, cover most *Candida* species, but lack reliable activity against *Candida krusei*. Fluconazole has limited or no activity against most moulds. Itraconazole coverage does not include all moulds and this agent has many drug–drug interactions. The newer broad-spectrum azole voriconazole has improved mould coverage, including efficacy against *P. boydii* and many *Fusarium* species, but still lacks activity against the Zygomycetes. Like itraconazole, this drug also has many drug–drug interactions. The echinocandins, anidulafungin, caspofungin and micafungin, are good agents for most *Candida* and *Aspergillus* species, but lack reliable coverage of the Zygomycetes, other less common moulds, as well as *Cryptococcus* and *Trichosporon* species. Of the currently approved agents, only amphotericin B has proven efficacy against the agents of zygomycosis (mucormycosis). This varying spectrum of activity emphasizes the importance of accurate identification of infecting fungi often down to the species level.

Cultures recovered fungi that correlated with the morphology seen on histopathology in the majority of cases (88%, 32/36). Among those specimens with *Aspergillus*-like morphology, all cultures recovered organisms, which could produce the described morphology in tissue. Unfortunately, if one limited the interpretation of correlation to *Aspergillus*-like morphology specimens only recovering *Aspergillus* species and Yeast-like morphology only yeasts, this correlation drops to 39% (14/36). There are a large number of common and uncommon fungal pathogens that can produce parallel-walled, septate hyphae (or structures that appear very similar) in tissue. In this study, we recovered *C. albicans*, *Candida parapsilosis*, *Bipolaris*, *Curvularia*, *Fusarium*, and *Trichosporon* species from cultures that corresponded to specimens with *Aspergillus*-like morphology on histopathology. Additionally, we found that cultures recovered multiple fungal organisms in association with 12 specimens. Clearly, there are several instances in our series in which empiric therapy based on histological appearance may have required a change in therapy once microbiological data was obtained. Of those patient identified with *Aspergillus*-like morphology on initial surgical pathology, empirical therapy with amphotericin B may have resulted in incomplete antifungal therapy in 35% (8/23) of cases (in which fungi such as *A. terreus*, *Trichosporon* and *Fusarium* species were recovered). The best histopathology-to-culture correlation was with *Candida*, in which 63% of specimens ultimately also grew a *Candida* species alone.

Limitations of this study include the retrospective nature of our study, the low numbers of FWI and FWC, and the limited number of cultures corresponding to the tissue with fungi by histopathology. Additionally, our data were likely affected by the known difficulties in culturing the infecting fungi from tissue specimens. Tissue grinding, used commonly in clinical microbiology laboratories to prepare samples for culture, is also widely believed to reduce recovery of the Zygomycetes. Recovery of most moulds is reportedly reduced by the use of swab cultures. Currently, no alternative molecular methods (e.g., DNA probes or PCR techniques) or direct immunohistochemistry are available to detect the wide variety of fungal pathogens. Thus, no good alternative to culture is available.

5. Conclusion

With the expanding armamentarium of antifungal agents with differing spectrums of activity it is becoming increasingly

important to correlate wound histopathology with corresponding cultures. Our study highlights that histopathology alone is often inadequate for determining the best antifungal agent as the histopathology-to-culture correlation was poor. As the fungi involved in FWI are common normal flora or environmental contaminants, the role of confirming infection with histopathology remains. However, with the data presented herein and the increased prevalence of fungi as etiologic agents of burn infection, emphasis should be given to ensure the best possible specimens are sent for fungal culture. Future study must focus on development of better diagnostic systems to identify fungi in tissues to the species level. Furthermore, our data highlight the importance of sending tissue for fungal culture at the same time as histopathological specimens when a diagnosis of fungal burn wound infection is suspected, allowing the best possible antifungal therapy to be selected.

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